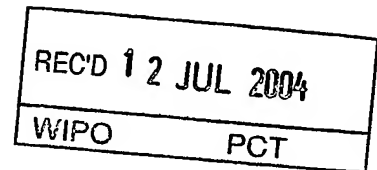


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## NOVEL IMIDAZOPYRIDINE COMPOUND II WITH THERAPEUTIC EFFECT

### TECHNICAL FIELD

The present invention relates to a novel compound, and therapeutically acceptable salts thereof, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compound; to pharmaceutical compositions containing the compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient; and to the use of the active compound in the manufacture of medicaments for the medical use indicated above.

### BACKGROUND ART

Substituted imidazo[1,2-a]pyridines, useful in the treatment of peptic ulcer diseases, are known in the art, e.g. from EP-B-0033094 and US 4,450,164 (Schering Corporation); from EP-B-0204285 and US 4,725,601 (Fujisawa Pharmaceutical Co.); from WO99/55706 and WO99/55705 (AstraZeneca); from WO 03/018582 (AstraZeneca); and from publications by J. J. Kaminski et al. in the Journal of Medical Chemistry (vol. 28, 876-892, 1985; vol. 30, 2031-2046, 1987; vol. 30, 2047-2051, 1987; vol. 32, 1686-1700, 1989; and vol. 34, 533-541, 1991).

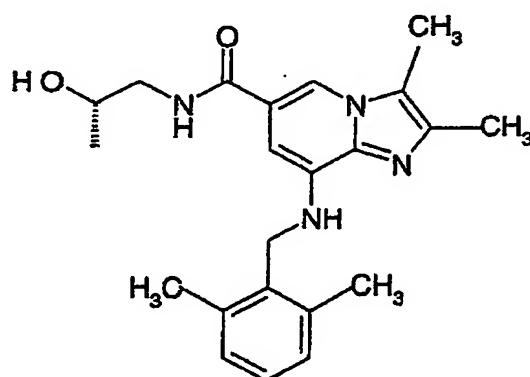
For a review of the pharmacology of the gastric acid pump (the  $H^+$ ,  $K^+$ -ATPase), see Sachs et al. (1995) Annu. Rev. Pharmacol. Toxicol. 35: 277-305.

We have now found an additional substituted imidazo[1,2-a]pyridine, useful in the treatment of peptic ulcer diseases exhibiting advantageous properties e.g. fast onset, high potency and/or long duration.

## DISCLOSURE OF THE INVENTION

It has surprisingly been found that compound of the Formula I is particularly effective as inhibitor of the gastrointestinal  $H^+$ ,  $K^+$ -ATPase and thereby as inhibitor of gastric acid secretion.

In one aspect, the present invention thus relates to a compound of Formula I



(I)

or a pharmaceutically acceptable salt thereof.

Depending on the process conditions the end product of the Formula I is obtained either in neutral or salt form. Both the free base and the salts of the end product are within the scope of the invention.

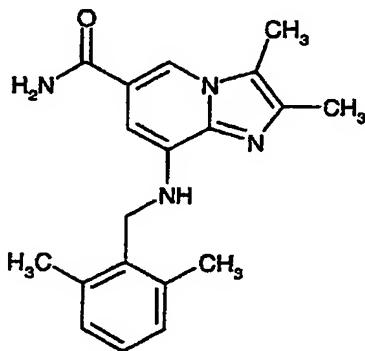
In the preparation of acid addition salts, preferably such acids are used which form therapeutically acceptable salts. Examples of such acids are hydrohalogen acids such as hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulphonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, p-hydroxybenzoic acid, embonic acid, methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid, halogenbenzenesulphonic acid, toluenesulphonic acid or naphthalenesulphonic acid.

## PREPARATION

- 5 The present invention also provides the following process for the manufacture of the compound with Formula I.

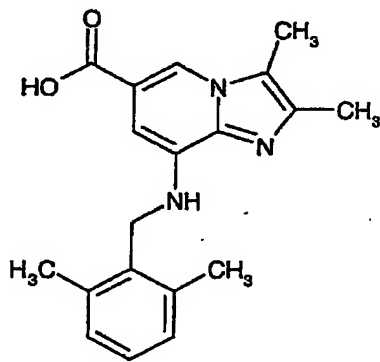
A process for manufacture of compound with Formula I comprises the following steps:

- a) Compound of Formula II



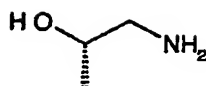
(II)

10 can be hydrolyzed under standard conditions to the corresponding carboxylic acid compound of Formula III



(III)

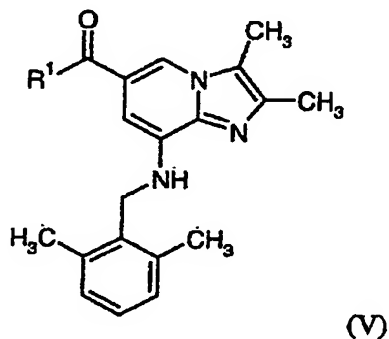
- 15 b) Compound of the Formula III can be reacted with amino compound of Formula IV



in the presence of a coupling reagent, such as *o*-be: (IV)  $\cdot N,N,N',N'$ -  
tetramethyluronium tetrafluoroborate (TBTU) to the corresponding amide compounds of  
the Formula I. The reaction can be carried out in an inert solvent under standard  
5 conditions.

An alternative process for manufacture of compound with Formula I comprises the  
following steps:

10 a) Compound of Formula V

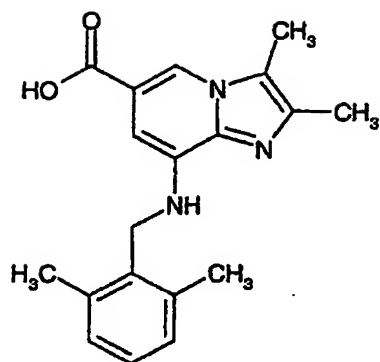


(V)

wherein  $R^1$  is a  $C_1$ - $C_6$ -alkoxy,

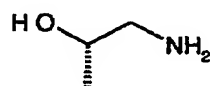
15 can be hydrolyzed under standard conditions to the corresponding carboxylic acid  
compound of Formula III

5



(III)

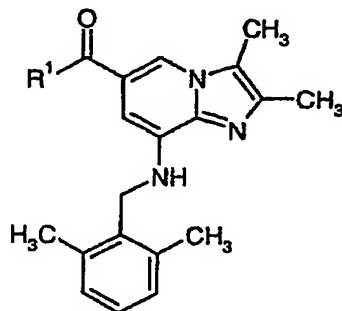
b) compound of the Formula III can be reacted with amino compound of Formula IV



(IV)

in the presence of a coupling reagent, such as o-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) to the corresponding amide compound of the Formula I. The reaction can be carried out in an inert solvent under standard conditions.

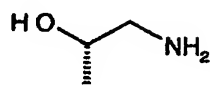
A further process for producing the compound of the invention comprises the following step  
compounds of the Formula (V),



(V)

wherein  $R^1$  is a  $C_1$ - $C_6$ -alkoxy,

can be reacted with an amino compound of Formula (IV)



(IV)

to give the corresponding amide compound of Formula I.

The reaction can be carried out by heating the reactants in the neat amino compound or dissolved in an inert solvent under standard conditions, e.g. in tetrahydrofuran (THF) at elevated temperature or at reflux.

#### MEDICAL USE

In a further aspect, the invention relates to the compound of the formula I for use in therapy, in particular for use against gastrointestinal inflammatory diseases. The invention also provides the use of a compound of the formula I in the manufacture of a medicament for the inhibition of gastric acid secretion, or for the treatment of gastrointestinal inflammatory diseases.

The compound according to the invention may thus be used for prevention and treatment of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome. Furthermore, the compound may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable, e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. The compound may also be used for effective control and treatment of heartburn and other GERD symptoms (acute and maintenance symptomatic GERD, erosive esophagitis healing and maintenance), heartburn, regurgitation, short and long-term management of acid reflux

disease and nausea. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration.

5 The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 1000 mg per day of active substance.

### PHARMACEUTICAL FORMULATIONS

10

In yet a further aspect, the invention relates to pharmaceutical compositions containing the compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient.

15 For clinical use, the compound of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. The pharmaceutical formulation contains a compound of the invention in combination with one or more pharmaceutically acceptable ingredients. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further  
20 object of the invention. Usually the amount of active compounds is between 0.1–95% by weight of the preparation, preferably between 0.1–20% by weight in preparations for parenteral use and preferably between 0.1 and 50% by weight in preparations for oral administration.

25 In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium  
30 stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets.



Soft gelatin capsules may be prepared with capsules containing the active compound of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatin capsules. Hard gelatin capsules may contain granules of the active compound. Hard gelatin capsules may also contain the active compound in combination with solid powdered ingredients such as  
5 lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance mixed with a neutral fat base; (ii) in the form of a  
10 gelatin rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatin rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

15 Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.1% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain coloring agents, flavoring agents, saccharine and carboxymethyl  
20 cellulose or other thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from  
25 0.1% to 10% by weight. These solutions may also contain stabilizing ingredients and/or buffering ingredients and are dispensed into unit doses in the form of ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

30

The compounds according to the invention can also be used in formulations together with other active ingredients, e.g. for the treatment or prophylaxis of conditions involving

infection by *Helicobacter pylori* of human gastric mucosa. Such other active ingredients may be antimicrobial agents, in particular:

- $\beta$ -lactam antibiotics such as amoxicillin, ampicillin, cephalothin, cefaclor or cefixime;
- macrolides such as erythromycin, or clarithromycin;
- 5   • tetracyclines such as tetracycline or doxycycline;
- aminoglycosides such as gentamycin, kanamycin or amikacin;
- quinolones such as norfloxacin, ciprofloxacin or enoxacin;
- others such as metronidazole, nitrofurantoin or chloramphenicol; or
- preparations containing bismuth salts such as bismuth subcitrate, bismuth subsalicylate,
- 10   bismuth subcarbonate, bismuth subnitrate or bismuth subgallate.

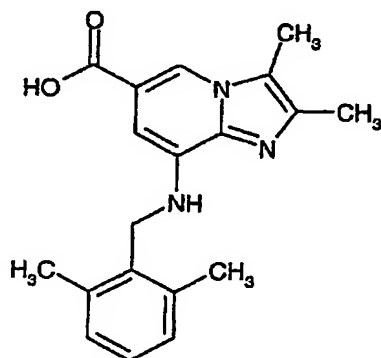
The compound according to the invention can also be used in formulations together with other active ingredients, e.g. for the treatment or prophylaxis of conditions involving medicament induced gastric ulcer. Such other active ingredients may be an NSAID, an  
15   NO-releasing NSAID, a COX-2 inhibitor or a bisphosphonate.

#### INTERMEDIATES

A further aspect of the invention is a new intermediate compound which are useful in the synthesis of the compound according to the invention.

20

Thus, the invention includes compound of Formula (III)



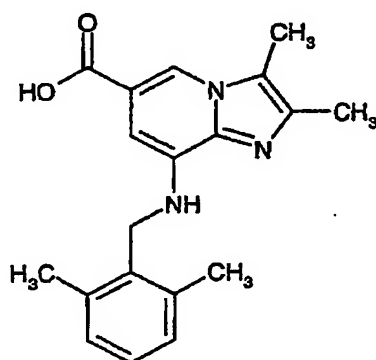
(III)

## EXAMPLES

## 5 1. PREPARATION OF THE COMPOUND OF THE INVENTION

*Example 1*

10 *Synthesis of 8-[(2,6-dimethylbenzyl)amino]-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid.*



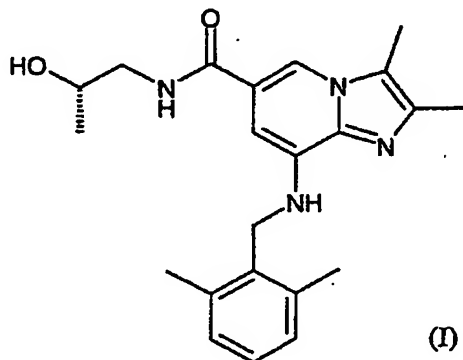
(III)

15 Isopropyl 8-[(2,6-dimethylbenzyl)amino]-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate (100 g, 0.274 mol) was added to methanol (900 ml) and water (100 ml). Sodium hydroxide (45 g, 1.13 mol) was added and the mixture was refluxed for 2 h. About half of the solvent was evaporated and the product was precipitated by adding acetic acid (100 ml) and water (1000 ml). The mixture was stirred over night at room temperature. The product was filtered of and washed with water and acetone. 88 g (99%) of the title  
20 compound was obtained.

<sup>1</sup>H NMR (DMSO, 400 MHz) δ 2.22 (s, 3H), 2.33 (s, 6H), 2.36 (s, 3H), 4.36 (d, 2H), 5.03 (t, 1H), 6.64 (s, 1H), 7.04-7.15 (m, 3H), 8.05 (s, 1H).

**Example 2**

8-[(2,6-dimethylbenzyl)amino]-N-[(2S)-2-hydroxypropyl]-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide



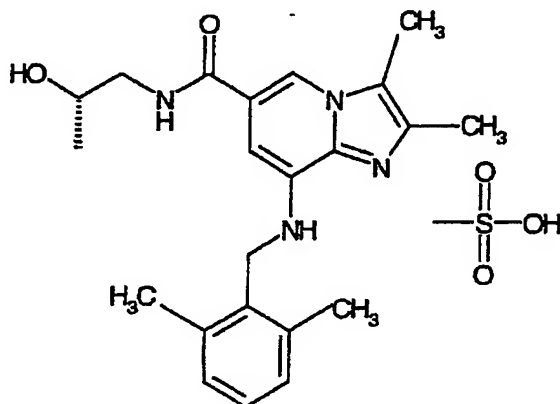
5 8-[(2,6-dimethylbenzyl)amino]-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid (30 g, 0.0928 mol) and 30 g diisopropylethylamine (30 g, 0.233 mol) were added to dimethylformamide (DMF) (250 ml). o-benzotriazol-1-yl-N, N, N',N'-tetramethyluronium tetrafluoroborate (TBTU) (36 g, 0.112 mol) was added. The mixture was stirred for 15 min at room temperature. S-1-amino-2-propanol (8.4 g, 0.112 mol) was added and the stirring  
10 was continued for 1 h at room temperature. Water (100 ml) was added and the reaction mixture was heated to 70 °C. The product was precipitated by slowly adding more water (200 ml). The mixture was then stirred for 5 h at 65-70 °C. After cooling to room temperature the product was filtered off and washed with 40% methanol solution. 33.7 g of the title compound was obtained.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.20 (d, 3H), 2.29 (s, 3H), 2.32 (s, 3H), 2.35 (s, 6H), 3.12-3.21 (m, 1H), 3.58-3.66 (m, 2H), 3.96-4.06 (m, 1H), 4.29 (d, 2H), 5.00 (t, 1H), 6.41 (s, 1H), 6.89 (t, 1H), 7.02-7.15 (m, 3H), 7.71 (s, 1H).

20

**Example 3**

**8-[(2,6-dimethylbenzyl)amino]-N-[(2S)-2-hydroxypropyl]-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate salt**



- 5 8-[(2,6-dimethylbenzyl)amino]-N-[(2S)-2-hydroxypropyl]-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide (29.0 g, 0.0762 mol) was dissolved in refluxing isopropanol (280 ml). Methanesulfonic acid (7.4 g, 0.0770 mol), dissolved in isopropanol (20 ml), was added to the solution. When cooled, a crystalline substance precipitated. The mixture was left over night at room temperature. The product was filtered off and washed with
- 10 isopropanol. 29.9 g of the title compound as mesylate salt was obtained.

<sup>1</sup>H NMR (DMSO, 500 MHz)  $\delta$  1.10 (d, 3H), 2.25 (s, 3H), 2.36 (s, 6H), 2.42 (s, 3H), 2.48 (s, 3H), 3.21-3.33 (m, 2H), 3.82-3.85 (m, 1H), 4.42 (d, 2H), 6.16 (s, 1H), 7.13-7.21 (m, 3H), 7.36 (s, 1H), 8.42 (s, 1H) 8.79 (t, 1H) 13.68 (bs, 1H).

## BIOLOGICAL TESTS

### *1. In vitro experiments*

#### 5 *Acid secretion inhibition in isolated rabbit gastric glands*

Inhibiting effect on acid secretion *in vitro* in isolated rabbit gastric glands was measured as described by Berglindh et al. (1976) Acta Physiol. Scand. 97, 401-414.

#### 10 *Determination of $H^+$ , $K^+$ -ATPase activity*

Membrane vesicles (2.5 to 5  $\mu$ g) were incubated for 15 min at +37°C in 18 mM Pipes/Tris buffer pH 7.4 containing 2 mM  $MgCl_2$ , 10 mM KCl and 2 mM ATP. The ATPase activity was estimated as release of inorganic phosphate from ATP, as described by LeBel et al.

15 (1978) Anal. Biochem. 85, 86-89.

### *2. In vivo experiments*

#### *Inhibiting effect on acid secretion in female rats*

20

Female rats of the Sprague-Dawley strain are used. They are equipped with cannulated fistulae in the stomach (lumen) and the upper part of the duodenum, for collection of gastric secretions and administration of test substances, respectively. A recovery period of 14 days after surgery is allowed before testing commenced.

25

Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed through the gastric cannula with tap water (+37°C), and 6 ml Ringer-Glucose given subcutaneously. Acid secretion is stimulated with infusion during 2.5-4 h (1.2 ml/h, subcutaneously) of pentagastrin and carbachol (20 and 110 nmol/kg·h, respectively), during which time gastric secretions are collected in 30-min fractions. Test substance or vehicle are given either at 60 min after starting the stimulation (intravenous

30

and intraduodenal dosing, 1 ml/kg), or 2 h before starting the stimulation (oral dosing, 5 ml/kg, gastric cannula closed). The time interval between dosing and stimulation may be increased in order to study the duration of action. Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 M, and acid output calculated as the product of titrant volume and concentration.

Further calculations are based on group mean responses from 4-6 rats. In the case of administration during stimulation; the acid output during the periods after administration of test substance or vehicle are expressed as fractional responses, setting the acid output in the 30-min period preceding administration to 1.0. Percentage inhibition is calculated from the fractional responses elicited by test compound and vehicle. In the case of administration before stimulation; percentage inhibition is calculated directly from acid output recorded after test compound and vehicle.

#### *Bioavailability in rat*

Adult rats of the Sprague-Dawley strain are used. One to three days prior to the experiments all rats are prepared by cannulation of the left carotid artery under anaesthesia. The rats used for intravenous experiments are also cannulated in the jugular vein (Popovic (1960) J. Appl. Physiol. 15, 727-728). The cannulas are exteriorized at the nape of the neck.

Blood samples (0.1 - 0.4 g) are drawn repeatedly from the carotid artery at intervals up to 5.5 hours after given dose. The samples are frozen until analysis of the test compound.

Bioavailability is assessed by calculating the quotient between the area under blood/plasma concentration (AUC) curve following (i) intraduodenal (i.d.) or oral (p.o.) administration and (ii) intravenous (i.v.) administration from the rat or the dog, respectively.

The area under the blood concentration vs. time curve, AUC, is determined by the log/linear trapezoidal rule and extrapolated to infinity by dividing the last determined

blood concentration by the elimination rate constant in the terminal phase. The systemic bioavailability ( $F\%$ ) following intraduodenal or oral administration is calculated as

$$F(\%) = (AUC \text{ (p.o. or i.d.)} / AUC \text{ (i.v.)}) \times 100.$$

5 *Inhibition of gastric acid secretion and bioavailability in the conscious dog.*

Labrador retriever or Harrier dogs of either sex are used. They are equipped with a duodenal fistula for the administration of test compounds or vehicle and a cannulated gastric fistula or a Heidenhaim-pouch for the collection of gastric secretion.

10

Before secretory tests the animals are fasted for about 18 h but water is freely allowed. Gastric acid secretion is stimulated for up to 6.5 h infusion of histamine dihydrochloride (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and gastric juice collected in consecutive 30-min fractions. Test substance or vehicle is given  
15 orally, i.d. or i.v., 1 or 1.5 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. In the case of oral administration, it should be pointed out that the test compound is administered to the acid secreting main stomach of the Heidenham-pouch dog.

20 The acidity of the gastric juice samples are determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or vehicle are expressed as fractional responses, setting the acid output in the fraction preceding administration to 1.0. Percentage inhibition is calculated from fractional responses elicited by test compound and vehicle.

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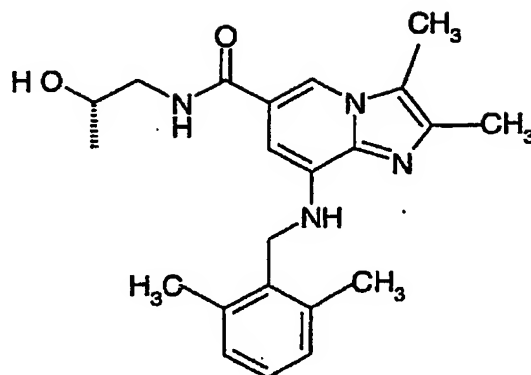
Blood samples for the analysis of test compound concentration in plasma are taken at intervals up to 4 h after dosing. Plasma is separated and frozen within 30 min after collection and later analyzed. The systemic bioavailability ( $F\%$ ) after oral or i.d. administration is calculated as described above in the rat model.

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## CLAIMS

1. A compound of formula I



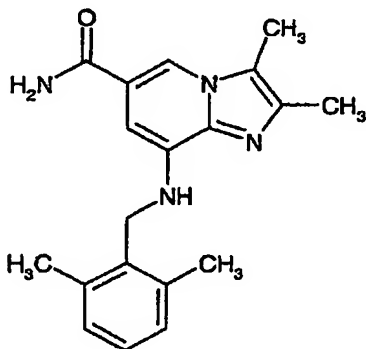
I

5 or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 being 8-[(2,6-dimethylbenzyl)amino]-N-[(2S)-2-hydroxypropyl]-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate salt.

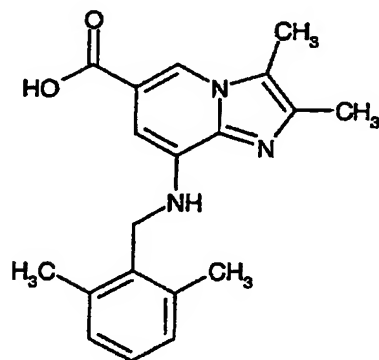
10 3. A process for the preparation of a compound according to any one of claims 1 and 2, comprising the steps of

a) treating a compound of Formula II



(II)

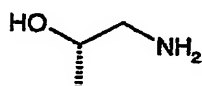
with acid or base under standard conditions to a compound of Formula III



(III)

b) reacting the compound of Formula III with a compound of Formula IV

5

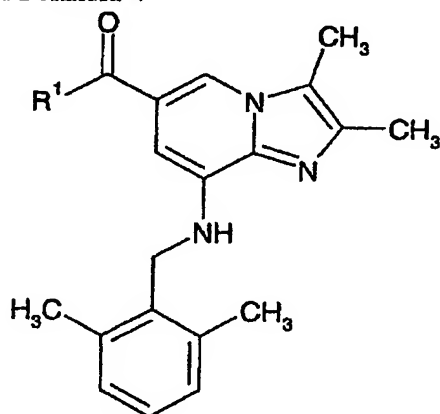


(IV)

in the presence of a coupling reagent in an inert solvent under standard conditions to give a compound of Formula I, or a pharmaceutically acceptable salt thereof.

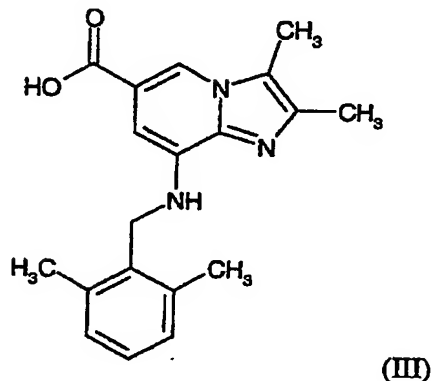
- 10 4. A process for the preparation of a compound according to any one of claims 1 and 2, comprising the steps of

a) treating a compound of Formula V

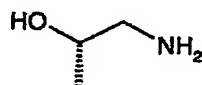


(V)

with acid or base under standard conditions to a compound of Formula III



- 5 b) reacting the compound of Formula III with a compound of Formula IV



(IV)

in the presence of a coupling reagent in an inert solvent under standard conditions to give a compound of Formula I.

10

5. A compound according to any one of claims 1 and 2 for use in therapy.

6. A pharmaceutical formulation containing a compound according to any one of claims 1 and 2 as active ingredient in combination with a pharmaceutically acceptable diluent or carrier.

15

7. Use of a compound according to any one of claims 1 and 2 for the manufacture of a medicament for the inhibition of gastric acid secretion.

20

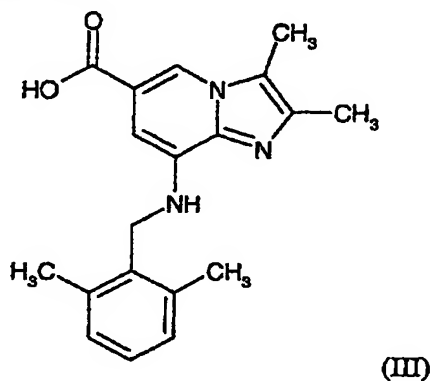
8. Use of a compound according to any one of claims 1 and 2 for the manufacture of a medicament for the treatment or prophylaxis of conditions involving infection by

*Helicobacter pylori* of human gastric mucosa, wherein the said compound is administered in combination with at least one antimicrobial agent.

9. A method for inhibiting gastric acid secretion which comprises administering to a mammal, including man, in need of such inhibition an effective amount of a compound according to any one of claims 1 and 2.

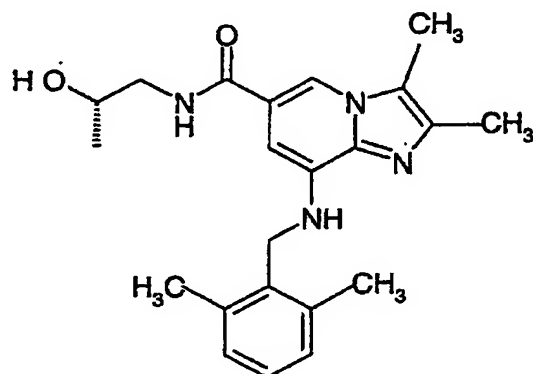
10. A method for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, which comprises administering to a mammal, including humans, in need of such treatment an effective amount of a compound as claimed in any one of claims 1 and 2, wherein the said salt is administered in combination with at least one antimicrobial agent.

11. A compound of the formula (III)



## ABSTRACT

The present invention relates to imidazo pyridine derivatives of the formula (I) which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used  
5 in the prevention and treatment of gastrointestinal inflammatory diseases.



(I)

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